REMARKS

I. Status of Claims

Claims 21-32 and 34-40 are pending and are under consideration in the present application. Claims 21-32 and 34-40 stand finally rejected under 35 U.S.C. §101 as lacking utility. Claims 21-32 and 34-40 also stand finally rejected under 35 U.S.C. §112, first paragraph, as not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 21 stands finally rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention.

II. Withdrawn Objections and Rejections

Applicants acknowledge with appreciation the Patent Office's withdrawal of the objections and several rejections presented in the previous Official Action. Specifically, the Patent Office has withdrawn the objection to the specification for not properly reciting SEQ ID NOs. Additionally, the Patent Office has withdrawn the objection to the specification for incorporating browser-executable code. Further, the Patent Office has withdrawn in part the rejection of claim 21 as indefinite. Lastly, the Patent Office has withdrawn the rejection of claims 37-40 for lack of written description.

III. Response to the Maintained Rejections of Claims 21-32 and 34-40 Under 35 U.S.C. §101 and 35 U.S.C. §112, First Paragraph

The Patent Office has maintained its rejection of claims 21-32 and 34 40 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. It remains the Patent Office's position that "no well-established utility exists for newly isolated complex biological molecules." Official Action, page 4. Summarily, it is the Patent Office's position that "[t]he skilled artisan is not provided with sufficient guidance to use the claimed polynucleotides for any purpose unique to this channel." Official Action, page 4. Applicants have carefully considered the Patent Office's comments presented in its Final Rejection. Applicants respectfully traverse the rejections and submit the following comments.

First, the Patent Office states that the fact patterns of the present case and that of Fujikawa v Wattanasin, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) are not parallel and therefore, the Patent Office contends, the holding in this case "is not significant or binding with regard to the instant rejections." Official Action, page 4. Applicants respectfully disagree. Applicants submit that even if that the fact patterns in the present case and Fujikawa might differ, at least one holding of the case remains applicable, namely, as applicants argued in the previous response, that "a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient." Fujikawa v Wattanasin, 93 F.3d 1559, 1565, 39 U.S.P.Q.2d 1895, 1900 (Fed. Cir. 1996). Moreover, applicants submit that while the invention described in Fujikawa may concern mevalonolactones, applicants believe this case is discussed in the Federal Register in the context of polynucleotides and polypeptides, rather than small molecules. Thus, applicants are of the opinion that Fujikawa is not limited to cases of chemical structures but is equally applicable to cases of novel polypeptides and polynucleotides as well.

Applicants again submit that adequate correlation between the claimed polynucleotides and polypeptides is presented in the Specification and as described in the previous Response. As stated in the Specification:

> K+betaM5, has significant homology at the nucleotide and amino acid level to the human Maxi-K potassium channel beta subunit, KCNMB1 (Genbank Accession No. gi|4758625; SEQ ID NO:98), the human potassium channel K+Hnov28 protein (K+Hnov28; Genbank Accession No. gi| Y34129; SEQ ID NO:3), the human lung protein (MGC:2376; Genbank Accession No. gi|12654469; SEQ ID NO:25), the human MSTP028 protein (MSTP028; Genbank Accession No. gi|11640564; SEQ ID NO:26); the Caenorhabditis K+ channel tetramerisation domain containing protein (K+channel_tetra; Genbank Accession No. gi|3875362; SEQ ID NO:28); and the Drosophila CG10465 protein (CG10465; Genbank Accession No. gi|7302243; SEQ ID NO:27). An alignment of the K+betaM5 polypeptide with these proteins is provided in Figures 7A-B.
>
> The K+betaM5 polypeptide was determined to share 20.0% identity and 40.0% similarity with the human Maxi-K potassium channel beta subunit, KCNMB1 (Genbank Accession No. gi|4758625; SEQ ID NO:98), to share 31.7% identity and 43.4% similarity with the human potassium channel K+Hnov28 protein (K+Hnov28; Genbank Accession No. gi| Y34129; SEQ ID NO:3), to share 34.4% identity and 45.6% similarity with the human lung protein, MGC:2376 (MGC:2376; Genbank Accession No. gi|12654469; SEQ ID NO:25), to share 31.7% identity and 43.4% similarity with the human MSTP028 protein (MSTP028; Genbank Accession No. gi|11640564; SEQ ID NO:26); to share 34.4% identity and 45.6% similarity with the Caenorhabditis K+ channel tetramerisation domain containing protein (K+channel_tetra; Genbank Accession

No. gi|3875362; SEQ ID NO:28); and to share 30.8% identity and 38.3% similarity with the Drosophila CG10465 protein (CG10465; Genbank Accession No. gi|7302243; SEQ ID NO:27) as shown in Figure 4.

Specification, page 47, line 34 to page 48, line 15. The Patent Office correctly interprets applicants arguments in this regard ("Applicants imply and discuss that homology of the disclosed polypeptide with a class of proteins already having utility shall impart sufficient utility on the novel polypeptide and on the polynucleotide encoding it." Official Action, page 9-10). Applicants submit that the disclosed homology with these proteins establishes utility for K+betaM5. The Patent Office apparently believes this may be the case with chemical structures, but not for novel polypeptides. The Patent Office, however, offers no authority, references or examples to support this position.

Next, the Patent Office addresses applicants' remarks regarding the various diseases applicants state can be treated by ligands of the claimed sequences. The Patent Office rebuts applicants' assertions with the statement that these diseases have "underlying etiologies that are unique and specific for each, and surely do not involve perturbations in the K+betaM5 peptide disclosed in the instant Application." Official Action, page 5. The Patent Office offers cystic fibrosis as an example of a well-characterized disease that is related to a particular mutation in a specific ion channel. The Patent Office then suggests that a similar identification/characterization of a disease with the K+betaM5 polypeptide could impart a function to the claimed polypeptide that would satisfy the Patent Office.

Respectfully, it is applicants' position that an adequate showing has been made in this regard. The Specification discloses at least those disease conditions identified by the Patent Office in the Official Action, all of which are known to involve ion channels. Applicants further submit that the Patent Office's statement that the identified conditions "surely do not involve perturbations in the K+betaM5 peptide" (Official Action, page 5) is unsubstantiated and is not supported by any reference. It therefore remains applicants' position that utility is established by the treatment of the cited conditions by ligands of the claimed polypeptide sequences.

Next the Patent Office responds to applicants' position that the use of the antibodies and immunohistochemistry methods described in the Specification provide still further utility for the claimed sequences. The Patent Office states "the usefulness of antibodies rests on the utility of the protein against which they are made." Applicants respectfully submit that the utility of the

K+betaM5 polypeptide itself is established in the Specification and highlighted in this and the previous Response. In view of this, applicants again submit that antibodies to K+betaM5 have a wide variety of applications, ranging, for example, from protein purification to therapeutic applications, which are discussed in the Specification.

The Patent Office then responds to applicants' arguments regarding the preparation of variants. The Patent Office maintains "[a]pplicant's arguments that one could merely test for activity is not sufficient for an enabling disclosure. Additionally, the Specification fails to teach which activity is possessed by the disclosed full-length non-variant polypeptide encoded by the K+betaM5 polynucleotide." Official Action, page 7. Applicants direct attention to, for example, page 3, lines 5-7, wherein applicants state, "[c]haracterization of the K+beta5 polypeptide of the present invention led to the determination that it is involved in negatively modulating the NFkB pathway, either directly or indirectly." This is just one example of an activity possessed by the disclosed full-length non-variant polypeptide encoded by the K+betaM5 polynucleotide. Applicants further submit that any testing that might be desirable in connection with such variants would be routine in nature, and methods for carrying out such tests would be well-known to those of ordinary skill in the art.

With regard to applicants' arguments that the precise nature of the binding site(s) of the K+betaM5 polypeptide of the present invention need not be known in order to practice the screening method claims presented in the instant patent application, the Patent Office maintains the discussion provided in the application is not substantial. The Patent Office premises its position on its belief that the claimed sequences have not been characterized. Applicants disagree with this position for the reasons presented herein. Applicants remain of the position that the claimed sequences have been characterized in numerous ways and to a degree sufficient to satisfy the statutory requirements of patentability.

Applicants restate their previous position that tissue typing is a specific, substantial and credible use for the claimed sequences. It is the Patent Office's position that this use is not specific because the claimed sequence is not associated with a particular tissue and that the association of the claimed sequences with the NF-κB pathway is not substantial because the pathway is a general once upon which many transduction pathways converge.

It remains applicants' position that tissue typing based on the claimed sequence is a specific, substantial and credible use, even if the claimed sequence is expressed in more than one

tissue. To the extent that the claimed sequences are expressed in more than one tissue, each of these tissues can be included in the typing profile, which represents a real-world use.

Applicants also remain of the opinion that the association with the NF-κB pathway presented in the Specification, even if this is a focal point of more than one transduction pathway, demonstrate the claimed sequences are useful for modulating this pathway. It is applicants' position that this utility stands on its own and that it is not relevant that other pathways might converge on the NF-κB pathway, as suggested by the Patent Office.

The Patent Office then discusses applicants' citation of *In re Brana* (51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995)). The Patent Office contends the main holding of *In re Brana* was that "FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws." Official Action, page 9. The Patent Office has asked for clarification of what is meant by applicants' discussion of this case. Initially applicants note that although it is agreed that *a* holding of *In re Brana* is that presented by the Patent Office in the Official Action, it is applicants' position that this is neither the *only* nor the *main* holding of this case.

The discussion of *In re Brana* was presented in support of applicants' position that one of ordinary skill in the art would not doubt the utility asserted by applicants and, therefore, that the claims are in compliance with 35 U.S.C. §101. More specifically, reiterating the language of *In re Brana*, applicants were arguing that "[o]nly after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility,"(*In re Brana*, 1566) and that it is applicants' position that the Patent Office did not present such evidence. Thus, in citing *In re Brana*, applicants were merely arguing, and reiterate now, that although applicants acknowledge the Patent Office's careful consideration and conscientious discussion of applicants' asserted utilities, applicants note that the Patent Office did not, and has not, presented documentary evidence to support its position that one of ordinary skill in the art would reasonably doubt the applicants' asserted utilities. Applicants duly note the Patent Office's statements regarding the asserted utilities but do not believe these opinions, absent documentary evidence, meet the minimum standards to support a rejection under 35 U.S.C. §101.

In view of this, it remains applicants' position that one of ordinary skill in the art would not reasonably doubt the asserted utilities. With due respect for the Patent Office's analysis of the asserted utilities, applicants remain of the opinion that the Patent Office has not provided "evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 1566.

Lastly, the Patent Office turns to applicants' remarks concerning enablement. Although applicants acknowledge the Patent Office's consideration of applicants' arguments related to the homology of the claimed sequences to other sequences, applicants remain of the opinion that the disclosure presented in the Specification is adequate to satisfy the requirements of 35 U.S.C. §112, first paragraph. It is applicants' position that the usefulness of the present invention provides much more than an "entry point" and speculative experiments, as suggested by the Patent Office. Applicants remain of the position that the claimed invention is fully enabled in view of at least the data presented in the Specification, such as homology data and RNAi data, and that "specific functional, physiological or pharmacological data" (Official Action, page 10) is not required in this regard. It remains applicants' position that in view of the identified utilities, the Specification, notably the Examples, provide the requisite disclosure to enable the invention as claimed.

Summarily, applicants again respectfully submit that, even in view of the Patent Office's analysis of applicants' asserted utility, the Patent Office has not presented evidence or sound scientific reasoning to rebut the assertion that K+betaM5 is a potassium ion channel subunit, which assertion is based, for example, on homology to a well-characterized class of nucleic acids and proteins, namely those presented in Figure 4 of the Specification and the assertion that, in one aspect, it is a useful target for the treatment of those disorders identified in the Specification. Applicants reiterate their position that the present application discloses and describes the biological role and significance of the claimed sequences having at least the utilities described in the previous Response.

Thus, although each patent application must be judged on its own merits, as the Patent Office indicates (Official Action, page 5), applicants submit that the specification in the present case presents at least one well-established and fully enabled use, as discussed herein. To the extent that each patent application must be judged on its own merits, applicants respectfully note

that there are inflexible statutory requirements related to utility and enablement, and applicants believe the present patent application has met these requirements.

In view of the above, applicants submit that the present patent application discloses at least one specific, substantial and credible utility. Accordingly, applicants respectfully request that the rejection of claims 21-32 and 34-40 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn. Applicants further submit that claims 21-32 and 34-40 are in condition for allowance and courteously solicit the same.

III. Response to the Rejection of Claim 21 Under 35 U.S.C. §112, Second Paragraph

Claim 21 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter that applicant regards as the invention. The Patent Office states that although the definition of "stringent" appears in the Specification, "the independent claim itself must define use of the word 'stringent'." Applicants have considered the Patent Office's comments and submit the following comments.

Applicants have amended claim 21 to incorporate the definition of the term "stringent," is found on page 74 of the Specification, and to which applicants direct attention for support for the amendment to claim 21.

Applicants submit that in view of the amendment of claim 21, claim 21 is now in full compliance with 35 U.S.C. §112, second paragraph. In view of the amendments, applicants respectfully request that the rejection of claim 21 under 35 U.S.C. §112, second paragraph be withdrawn. Applicants further submit claim 21 is in condition for allowance and courteously solicit the same.

IV. Conclusions

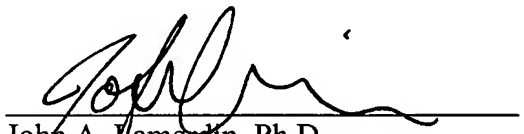
In light of the above amendments and remarks, applicants respectfully request that the present amendment be entered and that the rejections of record be withdrawn. Applicants further submit that the subject patent application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to

telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

If any fee is due in connection herewith not already accounted for, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment associated with the filing of this correspondence to Deposit Account Number 19-3880 in the name of the Bristol-Myers Squibb Company. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,



John A. Lamerdin, Ph.D.
Attorney for Applicants
Reg. No. 44,858

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-3575

Date: November 12, 2003